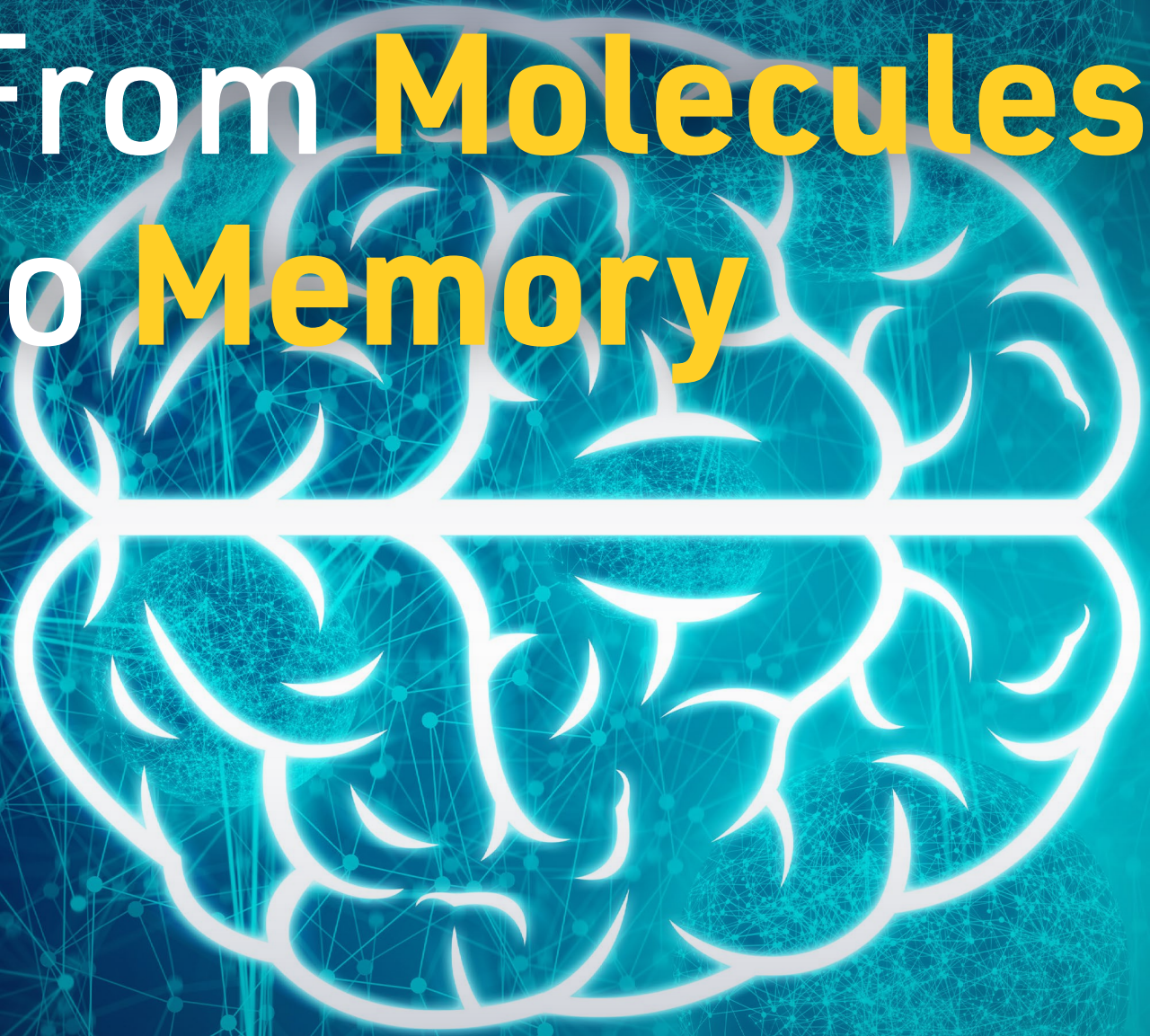
INSIDE

From Molecules to Memory



On a biological foundation of ions and proteins, the brain forms, stores, and retrieves memories to inform intelligent behavior. Pg. 8

Neuroscience News

WINTER 2024

THE PICOWER INSTITUTE
FOR LEARNING AND MEMORY

DIRECTOR'S **MESSAGE**

Dear Friends,

In the early 1990s Susumu Tonegawa decided to apply some of the latest techniques in molecular biology to the study of memory and in 1994–30 years ago–he launched a new center at MIT to recruit fellow scientists to that quest. In 2002, a transformative gift from Barbara and Jeffry Picower turned that center into The Picower Institute for Learning and Memory, and it's fair to say that over this history, we've learned quite a bit about the biology of memory.

So how does the assemblage of molecules we call a brain endow each of us not only with a rich recollection of our unique past, but also enable us to apply that knowledge to our future? Research is by no means complete, but neuroscientists hypothesize is that at its most fundamental levels, the brain builds itself to be flexible and adaptable, or "plastic," enabling us to take in new information and continually process it for intelligent use down the road. In our cover story (page 8), Biology Department writer Noah Daly asked four of our faculty members–Susumu, Troy Littleton, Elly Nedivi and Matt Wilson–who study this at different scales explain how the brain's "plasticity" may enable the storage and intelligent use of memory.

Memory is just one of the mysteries of the brain we aim to help solve. Two new studies, for example, examine different aspects of the question: What is the nature of perception amid unconsciousness? In one case (p.3) the findings of Earl Miller's team tell us more about how consciousness works and in the other (p.4) the insights of Emery Brown's team could help anesthesiologists better manage surgical pain.

It turns out that the lead authors of both of those studies were young women. At the Kuggie Vallee Distinguished Lectures and Workshop we hosted in September (p.6), we celebrated the successes of women in science even as we also discussed headwinds that remain.

All of us at The Picower Institute wish you a happy Holiday Season. We hope you can find your own reasons to celebrate and make joyful new memories.

LI-HUEI TSAI, DIRECTOR

The Picower Institute for Learning and Memory

How **40Hz** sensory stimulation may save 'white matter'

Early-stage trials in Alzheimer's disease patients and studies in mouse models have suggested positive impacts on pathology and symptoms from exposure to light and sound presented at the "gamma" band frequency of 40 Hz. A new study in *Nature Communications* zeroes in on how 40Hz sensory stimulation helps to sustain an essential process in which the signal-sending branches of neurons, called axons, are wrapped in a fatty insulation called myelin. Often called the brain's "white matter," myelin protects axons and insures better electrical signal transmission in brain circuits.

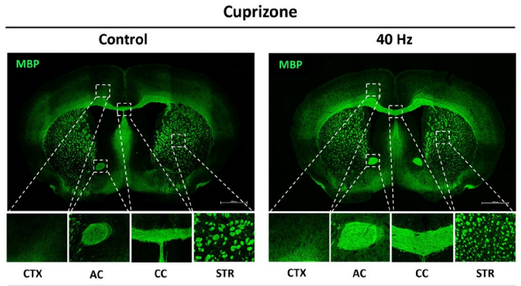
"Previous publications from our lab have mainly focused on neuronal protection," said Picower Professor and senior author Li-Huei Tsai. Tsai also leads MIT's Aging Brain Initiative. "But this study shows that it's not just the gray matter, but also the white matter that's protected."

This year Cognito Therapeutics, the spin-off company that licensed MIT's sensory stimulation technology, published phase II human trial results in the *Journal of Alzheimer's Disease* indicating that 40Hz light and sound stimulation significantly slowed the loss of myelin in volunteers with Alzheimer's. Also this year Tsai's lab published a study showing that gamma sensory stimulation helped mice withstand neurological effects of chemotherapy medicines, including by preserving myelin. In the new study, members of Tsai's lab led by former postdoc Daniela Rodrigues Amorim used a common mouse model of myelin loss—a diet with the chemical cuprizone— to explore how sensory stimulation preserves myelination.

Amorim and Tsai's team found that 40Hz light and sound not only preserved myelination in the brains of cuprizone-exposed mice, it also appeared to protect oligodendrocytes (the cells that myelinate neural axons), sustain the electrical performance of neurons, and preserve a key marker of axon structural integrity. When the team looked into the molecular underpinnings of these benefits, they found clear signs of specific mechanisms including preservation of neural circuit connections called synapses; a reduction in a cause of oligodendrocyte death called "ferroptosis;" reduced inflammation; and an increase in the ability of microglia brain cells to clean up myelin damage so that new myelin could be restored.

The findings suggest that gamma sensory stimulation may help not only Alzheimer's disease patients but also people battling other diseases involving myelin loss, such as multiple sclerosis, the authors wrote in the study.

To conduct the study, Tsai and Amorim's team fed some male mice a diet with cuprizone and gave other male mice a normal diet for six weeks. Halfway into that period, when cuprizone is known to begin causing its most acute effects on myelination, they exposed some mice from each group to gamma sensory stimulation for the remaining three weeks. In this way they had four groups: completely unaffected mice, mice that received no cuprizone but did get gamma stimulation, mice that received cuprizone and constant (but not 40Hz) light and sound as a control, and mice that received cuprizone and also gamma stimulation.



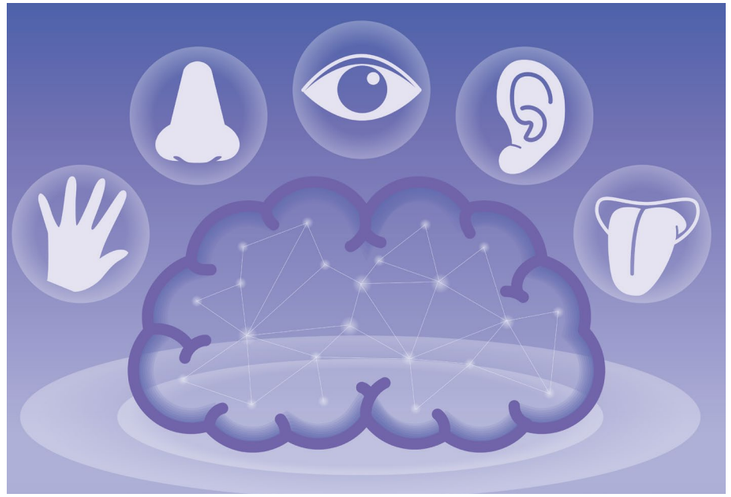
Among mice fed cuprizone to degrade myelination, 40Hz-treated mice retained more myelin in four key brain regions as indicated by green staining.

After the six weeks elapsed, the scientists measured signs of myelination throughout the brains of the mice in each group. Mice that weren't fed cuprizone maintained healthy levels, as expected. Mice that were fed cuprizone and didn't receive 40Hz gamma sensory stimulation showed drastic levels of myelin loss. Cuprizone-fed mice that received 40Hz stimulation retained significantly more myelin, rivaling the health of mice never fed cuprizone by some, but not all, measures.

Sensory prediction changes under anesthesia indicate how **consciousness** works

Our brains constantly work to make predictions about what's going on around us, for instance to ensure that we can attend to and consider the unexpected. A new study examines how this works during consciousness and also breaks down under general anesthesia. The results add evidence for the idea that conscious thought requires synchronized communication—mediated by brain rhythms in specific frequency bands—between basic sensory and higher-order cognitive regions of the brain.

Previously, members of the research team at The Picower Institute and Vanderbilt University had described how brain rhythms enable the brain to remain prepared to attend to surprises. Cognition-oriented brain regions (generally at the front of the brain), use relatively low frequency alpha and beta rhythms to suppress processing by sensory regions (generally toward the back of the brain) of stimuli that have become familiar and mundane in the environment (e.g. your co-worker's music). When sensory regions detect a surprise (e.g. the office fire alarm), they use faster frequency gamma rhythms to tell the higher regions about it and the higher regions process that at gamma frequencies to decide what to do (e.g. exit the building).



The new results in the *Proceedings of the National Academy of Sciences*, show that when animals were under propofol-induced general anesthesia, a sensory region retained the capacity to detect simple surprises, but communication with a higher cognitive region toward the front of the brain was lost. The frontal region became unable to engage in its "top-down" regulation of the activity of the sensory region and remained oblivious to simple and more complex surprises alike.

"What we are doing here speaks to the nature of consciousness," said Picower Professor and co-senior author Earl K. Miller. "Propofol general anesthesia deactivates the top-down processes that underlie cognition. It essentially disconnects communication between the front and back halves of the brain."

Co-senior author Andre Bastos, an assistant professor in the psychology department at Vanderbilt and a former member of Miller's MIT lab, added that the study results highlight the key role of frontal areas in consciousness.

"It was interesting that the front of the brain, areas associated with cognition, were more strongly diminished in their predictive abilities than sensory areas," Bastos said. "This suggests that prefrontal areas help to spark an 'ignition' event that allows sensory information to become conscious. Sensory cortex activation by itself does not lead to conscious perception. These observations help us narrow down possible models for the mechanisms of consciousness."

To conduct the research, the neuroscientists measured the electrical signals, or "spiking," of hundreds of individual neurons and the coordinated rhythms of their aggregated activity (at alpha/beta and gamma frequencies), in two areas on the surface, or cortex, of the brain of two animals as they listened to sequences of tones. Sometimes the sequences would all be the same note, (e.g. AAAAA). Sometimes there'd be a simple surprise that the researchers called a "local oddball" (e.g. AAAAB). But sometimes the surprise would be more complicated, or a "global oddball." For example, after seeing a series of AAAABs, there'd all of a sudden be AAAAA, which violates the global, but not the local, pattern.

Prior work has suggested that a sensory region (the "Tpt") can spot local oddballs on its own, Miller said. Detecting the more complicated global oddball requires the participation of a higher order region (the "FEF").

The animals heard the tone sequences both while awake and while under propofol anesthesia. By several measures and analyses, the scientists could see these dynamics during wakefulness break down after the animals lost consciousness.

Under propofol, for instance, spiking activity declined overall but when a local oddball came along, Tpt spiking still increased notably but now spiking in FEF didn't follow suit as it does during wakefulness.

When a global oddball occurred during wakefulness, the researchers could use software to "decode" representation of that among neurons in FEF and the prefrontal cortex (another cognition-oriented region). They could also decode local oddballs in the Tpt. But under anesthesia the decoder could no longer reliably detect representation of local or global oddballs in FEF or the prefrontal cortex.

Moreover, when they compared rhythms in the regions amid wakeful vs. unconscious states they found stark differences. When the animals were awake, oddballs increased gamma activity in both Tpt and FEF and alpha/beta rhythms decreased. Regular, non-oddball stimulation increased alpha/beta rhythms. But when the animals lost consciousness the increase in gamma rhythms from a local oddball was even greater in Tpt than when the animal was awake.

Quantifying "nociception" could improve surgical **pain** management

The degree to which a surgical patient's subconscious processing of pain, or "nociception," is properly managed by their anesthesiologist will directly affect the degree of post-operative drug side effects they'll experience and the need for further pain management they'll require. But pain is a subjective feeling to measure, even when patients are awake, much less when they are unconscious. In a new study, MIT and Massachusetts General Hospital (MGH) researchers describe a set of statistical models that objectively quantified nociception during surgery. Ultimately, they hope to help anesthesiologists optimize drug dose and minimize post-operative pain and side effects.

The new models integrate data meticulously logged over 18,582 minutes of 101 abdominal surgeries in men and women at MGH. Led by former MIT graduate student Sandya Subramanian, now an assistant professor at UC Berkeley and UC San Francisco, the researchers collected and analyzed data from five physiological sensors as patients experienced a total of 49,878 distinct "nociceptive stimuli" (such as incisions or cautery). Moreover, the team recorded what drugs were administered, and how much and when, to factor in their effects on nociception or cardiovascular measures. They then used all the data to develop a set of statistical models that performed well in retrospectively indicating the body's response to nociceptive stimuli.

The team's goal is to furnish such accurate, objective, and physiologically principled information in real-time to anesthesiologists who currently have to rely heavily on intuition and past experience in deciding how to administer pain-control drugs during surgery. If anesthesiologists give too much, patients can experience side effects ranging from nausea to delirium. If they give too little, patients may feel excessive pain after they awaken.

"Sandya's work has helped us establish a principled way to understand and measure nociception during general anesthesia," said study senior author Emery N. Brown, Edward Hood Taplin Professor of Medical Engineering and Computational Neuroscience in The Picower Institute. Brown is also an anesthesiologist at MGH. "Our next objective is to make the insights that we have gained from Sandya's studies reliable and practical for anesthesiologists to use during surgery."

The research began as Subramanian's doctoral thesis project in Brown's lab in 2017. The best prior attempts to objectively model nociception have either relied solely on the electrocardiogram (ECG, an indirect indicator of heart-rate variability) or other systems that may incorporate more than one measurement, but were either based on lab experiments using pain stimuli that do not compare in intensity to surgical pain or were validated by statistically aggregating just a few time points across multiple patients' surgeries, Subramanian said.

"There's no other place to study surgical pain except for the operating room," Subramanian said. "We wanted to not only develop the algorithms using data from surgery, but also actually validate it in the context in which we want someone to use it. If we are asking them to track moment-to-moment nociception during an individual surgery, we need to validate it in that same way."

So she and Brown worked to advance the state of the art by collecting multi-sensor data during the whole course of actual surgeries and by accounting for the confounding effects of the drugs administered. In that way, they hoped to develop a model that could make accurate predictions that remained valid for the same patient all the way through their operation.

Part of the improvements the team achieved arose from tracking patterns of heart rate and also skin conductance. Changes in both of these physiological factors can be indications of the body's primal "fight or flight" response to nociception or pain, but some drugs used during surgery directly affect cardiovascular state, while skin conductance (or "EDA," electrodermal activity) remains unaffected. The study measures not only ECG but also backs it up with PPG, an optical measure of heart rate (like the oxygen sensor on a smartwatch), because ECG signals can sometimes be made noisy by all the electrical equipment buzzing away in the operating room. Similarly, Subramanian backstopped EDA measures with measures of skin temperature to ensure that changes in skin conductance from sweat were because of nociception and not simply the patient being too warm. The study also tracked respiration.

Then the authors performed statistical analyses to develop physiologically relevant indices from each of the cardiovascular and skin conductance signals. And once each index was established, further statistical analysis enabled tracking the indices together to produce models that could make accurate, principled predictions of when nociception was occurring and the body's response.

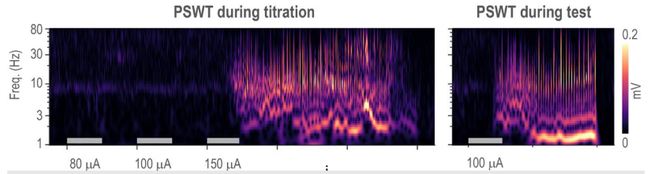
Study assesses **seizure** risk from stimulating thalamus

The idea of electrically stimulating the brain's central thalamus has gained traction among researchers and clinicians because it can help arouse subjects from unconscious states induced by traumatic brain injury or anesthesia, and can boost cognition and performance in awake animals. But the method, called CT-DBS, can have a side effect: seizures. A new study by researchers at MIT and Massachusetts General Hospital (MGH) who were testing the method in awake mice quantifies the probability of seizures at different stimulation currents and cautions that they sometimes occurred at low levels.

"Understanding production and prevalence of this type of seizure activity is important because brain stimulation-based therapies are becoming more widely used," said co-senior author Emery N. Brown, Edward Hood Taplin Professor of Medical Engineering and Computational Neuroscience.

The researchers were hoping to determine a CT-DBS stimulation current— in a clinically relevant range of under 200 microamps— below which seizures could be reliably avoided.

In search of that ideal current, they developed a protocol of starting brief bouts of CT-DBS at 1 microamp and then incrementally ramping the current up to 200 microamps until they found a threshold where a seizure occurred. Once they found that threshold, then they tested a longer bout of stimulation at the next lowest current level in hopes that an electrographic seizure wouldn't occur. They did this for a variety of different stimulation frequencies. To their surprise, electrographic seizures still occurred 2.2 percent of the time during those longer stimulation trials (i.e. 22 times out of 996 tests) and in 10 out of 12 mice. At just 20 microamps, mice still experienced them in 3 out of 244 tests, a 1.2 percent rate.



Researchers progressively titrated current (horizontal axis). Here during titration (left panel), a mouse experienced a seizure (a burst of higher voltages at a broad spread of frequencies) at 150 microamps. When the researchers applied a test current at 100 microamps for a longer time (right panel), a seizure occurred as well.

"This is something that we needed to report because this was really surprising," said co-lead author Francisco Flores, a research affiliate in The Picower Institute and an instructor in anesthesiology at MGH where Brown is also an anesthesiologist. Isabella Dalla Betta, a technical associate in The Picower Institute, co-led the study published in *Brain Stimulation.*

Stimulation frequency didn't matter for seizure risk but the rate of electrographic seizures increased as the current level increased. For instance, it happened in 5 out of 190 tests at 50 microamps, and 2 out of 65 tests at 100 microamps. The researchers also found that when an electrographic seizure occurred, it did so more quickly at higher currents than at lower levels. Finally, they also saw that seizures happened more quickly if they stimulated the thalamus on both sides of the brain vs. just one side.

Secrets of neural **longevity** could benefit the aging brain and body

Neurons in the brain can live for more than 90 years, making them exceptional examples of longevity among cells, but scientists know little about how neurons achieve that long lifespan. With a new Glenn Foundation Discovery Award, Myriam Heiman, John and Dorothy Wilson Associate Professor of Neuroscience, and her lab plan a research project that will expand on preliminary work aimed at discovering the genetic and molecular basis of neural longevity.

Heiman has long studied the mechanisms that make different cells in the brain especially vulnerable amid neurodegenerative diseases such as Parkinson's disease, Huntington's Disease, ALS, and frontotemporal dementia. She said that observing the molecular markers of aging in such diseases inspired her to examine aging and longevity in neurons more fundamentally.

Support from the award, $525,000 over three years from Glenn Foundation for Medical Research (GFMR) and the American Federation for Aging Research (AFAR), will enable Heiman's lab to conduct rigorous and unbiased testing in the mammalian nervous system to discover genes that underly neural longevity and might restore aging-associated decline in nerve cells.

"The mechanisms that underlie the exceptional longevity of nerve cells in our brain remain unclear," Heiman said. "If they were understood, however, they could be targeted to restore nerve cell function in the context of aging and neurodegeneration, and they could also potentially be induced in other cell types of the body to increase the healthspan of the whole organism."

Heiman said she was very grateful for the award, which will enable her and her team members to pursue this research project.

"AFAR and GFMR are the leading funders of new and innovative scientific research in the aging field," Heiman said. "Their mission in this area is of great importance, since elucidating aging mechanisms at the basic scientific level will lead the way to tremendous advances in the treatment of innumerable age-associated diseases. Receiving this grant now has enabled work at a crucial early stage."

Mixing joy and resolve, event celebrates **women** in science and addresses persistent inequalities

For two days at The Picower Institute, participants in the Kuggie Vallee Distinguished Lectures and Workshops celebrated the success of women in science and shared strategies to persist through, or better yet dissipate, the stiff headwinds women still face in the field.

"Everyone is here to celebrate and to inspire and advance the accomplishments of all women in science," said host Li-Huei Tsai, Picower Professor and director of The Picower Institute, as she welcomed scores of students, postdocs and other research trainees. "It is a great feeling to have the opportunity to showcase examples of our successes and to help lift up the next generation."

Tsai hosted the event after being named a Vallee Visiting Professor in 2022 by the Vallee Foundation. Foundation President Peter Howley, a professor at Harvard, said the global series of lectureships and workshops were created to honor Kuggie Vallee, a former Lesley College Professor who worked to advance the careers of women.

A panel of leading women scientists: (l. to r.) Michelle Monje, Susan Silbey, Kara McKinley, Erin Schuman, Stacey Weninger, and moderator Elly Nedivi, William R. and Linda R. Young Professor in The Picower Institute

During the program Sept. 24-25, speakers and audience members alike made it clear that helping women succeed requires both recognizing their achievements and resolving to change social structures in which they face marginalization.

Lectures on the first day featured two brain scientists who have each led acclaimed discoveries that have been transforming their fields.

Michelle Monje, a pediatric neuro-oncologist at Stanford whose recognitions include a MacArthur Fellowship, described her lab's studies of brain cancers in children, which emerge at specific times in development as young brains adapt to their world by wiring up new circuits and insulating neurons with a fatty sheathing called myelin. Monje has discovered that when the precursors to myelinating cells called oligodendrocyte precursor cells harbor cancerous mutations, the tumors that arise—called gliomas—can hijack those cellular and molecular mechanisms. To promote their own growth, gliomas tap directly into the electrical activity of neural circuits by forging functional neuron-to-cancer connections, akin to the "synapse" junctions healthy neurons make with each other. Her studies, often led by female trainees, have not only revealed this insidious behavior (and linked aberrant myelination to many other diseases), but also revealed specific molecular factors involved. Those findings, Monje said, present completely novel potential avenues for therapeutic intervention.

"This cancer is an electrically active tissue and that is not how we have been approaching understanding it," she said.

Erin Schuman, who directs the Max Planck Institute for Brain Research in Frankfurt and has won honors including the Brain Prize, described her groundbreaking discoveries related to how neurons form and edit synapses along the very long branches—axons and dendrites—that give the cells their exotic shapes. Synapses form very far from the cell body where scientists had long thought all proteins, including those needed for synapse structure and activity, must be made. In the mid-1990s Schuman showed that the protein-making process can occur at the synapse and that neurons stage the needed infrastructure—mRNA and ribosomes—near those sites. Her lab has continued to develop innovative tools to build on that insight, cataloging the stunning array of thousands of mRNAs involved, including about 800 that are primarily translated at the synapse, studying the diversity of synapses that arise from that collection, and imaging individual ribosomes such that her lab can detect when they are actively making proteins in synaptic neighborhoods.

While first day showcased women's success, the second day's workshops turned the spotlight on the social and systemic hindrances that continue to make such achievements an uphill climb. Speakers and audience members engaged in frank dialogues aimed at calling out those barriers, overcoming them, and dismantling them.

Susan Silbey, Leon and Anne Goldberg Professor of Humanities, Sociology and Anthropology at MIT and Professor of Behavioral and Policy Sciences in the Sloan School of Management, said that as bad as sexual harassment and assault in the workplace are, the more pervasive, damaging and persistent headwinds for women across a variety of professions are "deeply sedimented cultural habits" that marginalize their expertise and contributions in workplaces, rendering them invisible to male counterparts, even when they are in powerful positions. High-ranking women in Silicon Valley who answered the "Elephant in the Valley" survey, for instance, reported high rates of demeaning comments and conduct, as well as exclusion from social circles. Even Supreme Court justices are not immune, she noted, citing research showing that for decades female justices have been interrupted with disproportionate frequency during oral arguments at the court. Silbey's research has shown that young women entering the engineering workforce often become discouraged by a system that appears meritocratic but in which they are often excluded from opportunities to demonstrate or be credited for that merit and are paid significantly less.

"Women's occupational inequality is a consequence of being ignored, having contributions overlooked or appropriated, of being assigned to lower status roles, while men are pushed ahead, honored and celebrated, often on the basis of women's work," Silbey said.

Often relatively small in numbers, women in such workplaces become tokens—visible as different but still treated as outsiders, Silbey said. Women tend to internalize this status, becoming very cautious about their work while some men surge ahead in more cavalier fashion. Silbey and speakers who followed illustrated the effect this can have on women's careers in science. Kara McKinley, an assistant professor of stem cell and regenerative biology at Harvard, noted that while the scientific career "pipeline" in some areas of science is full of female graduate students and postdocs, only about 20 percent of natural sciences faculty positions are held by women. Strikingly, women are already significantly depleted in the applicant pools for assistant professor positions, she said. Those who do apply tend to wait until they are more qualified than the men they are competing against. McKinley and Silbey each noted that women scientists submit fewer papers to prestigious journals, with Silbey explaining that it's often because women are more likely to worry that their studies need to tie up every loose end. Yet, said Stacie Weninger, a venture capitalist and president of the F-Prime Biomedical Research Initiative and a former editor at Cell Press, women were also less likely than men to rebut rejections from journal editors, thereby accepting the rejection even though rebuttals sometimes work.

Several speakers including Weninger and Silbey said pedagogy must change to help women overcome a social tendency to couch their assertions in caveats when many men speak with confidence and are therefore perceived as more knowledgeable.

At lunch, trainees sat in small groups with the speakers. They shared sometimes harrowing personal stories of gender-related difficulties in their young careers and sought advice on how to persist and remain resilient. Schuman advised the trainees to report mistreatment, even if they aren't confident that university officials will be able to effect change, at least to make sure patterns of mistreatment get on the record. Reflecting on discouraging comments she experienced early in her career, Monje advised students to build up and maintain an inner voice of confidence and draw upon it when criticism is unfair.

"It feels terrible in the moment, but cream rises," Monje said. "Believe in yourself. It will be OK in the end."

Speakers at the conference shared many ideas to help overcome inequalities. McKinley described a program she launched in 2020 to ensure that a diversity of well-qualified women and non-binary postdocs are recruited for and apply for life sciences faculty jobs: the Leading Edge Symposium. The program identifies and names fellows—200 so far—and provides career mentoring advice, a supportive community, and a platform to ensure they are visible to recruiters. Since the program began, 99 of the fellows have gone on to accept faculty positions at various institutions.

Tracing the arc of her career, Weninger, who trained as a neuroscientist at Harvard, said she left lab bench work for a job as an editor because she wanted to enjoy the breadth of science, but also noted that her postdoc salary didn't even cover the cost of child care. She left Cell Press in 2005 to help lead a task force on women in science that Harvard formed in the wake of comments by then-president Lawrence Summers widely understood as suggesting that women lacked "natural ability" in science and engineering. The task force recommended steps to increase the number of senior women in science, including providing financial support for researchers who were also caregivers at home so they'd have the money to hire a technician. That extra set of hands could help them keep research running even as they also attended to their families. Notably, Monje said she does this for the postdocs in her lab.

Keynote speaker Erin Schuman

A graduate student asked Silbey at the end of her talk how to change a culture in which traditionally male-oriented norms marginalize women. Silbey said it starts with calling out those norms and recognizing that they are the issue, rather than increasing women's representation in, or asking them to adapt to, existing systems.

"To make change it requires that you do recognize the differences of the experiences and not try to make women exactly like men or continue the past practices and think, 'Oh, we just have to add women into it'," she said.

Silbey also praised the Kuggie Vallee event for assembling a community around these issues. Women in science need more social networks where they can exchange information and resources, she said.

"This is where an organ, an event like this, is an example of making just that kind of change: women making new networks for women," she said.

From Molecules to Memory

On a biological foundation of ions and proteins, the brain forms, stores, and retrieves memories to inform intelligent behavior.

Special feature by Noah Daly,
MIT Biology Department

Whenever you go out to a restaurant to celebrate, your brain retrieves memories while forming new ones. You notice the room is elegant, that you're surrounded by people you love, having meaningful conversations, and doing it all with good manners. Encoding these precious moments (and not barking at your waiter, expecting dessert before your appetizer), you rely heavily on plasticity, the ability of neurons to change the strength and quantity of their connections in response to new information or activity. The very existence of memory and our ability to retrieve it to guide our intelligent behavior are hypothesized to be movements of a neuroplastic symphony, manifested through chemical processes occurring across vast, interconnected networks of neurons.

During infancy, brain connectivity grows exponentially, rapidly increasing the number of synapses between neurons, some of which are then pruned back to select the most salient for optimal performance. This exuberant growth followed by experience-dependent optimization lays a foundation of connections to produce a functional brain, but the action doesn't cease there. Faced with a lifetime of encountering and integrating new experiences, the brain will continue to produce and edit connections throughout adulthood, decreasing or increasing their strength to ensure that new information can be encoded.

There are a thousand times more connections in the brain than stars in the Milky Way galaxy. Neuroscientists have spent more than a century exploring that vastness for evidence of the biology of memory. In the last 30 years, advancements in microscopy, genetic sequencing and manipulation, and machine learning technologies have enabled researchers, including four MIT Professors of Biology working in The Picower Institute for Learning and Memory – Elly Nedivi, Troy Littleton, Matthew Wilson, and Susumu Tonegawa – to help refine and redefine our understanding of how plasticity works in the brain, what exactly memories are, how they are formed, consolidated, and even changed to suit our needs as we navigate an uncertain world.

Circuits and Synapses: Our Information Superhighway

Neuroscientists hypothesize that how memories come to be depends on how neurons are connected and how they can rewire these connections in response to new experiences and information. This connectivity occurs at the junction between two neurons, called a synapse. When a neuron wants to pass on a signal, it will release chemical messengers called neurotransmitters into the synapse cleft from the end of a long protrusion called the axon, often called the "pre-synaptic" area.

These neurotransmitters, whose release is triggered by electrical impulses called action potentials, can bind to specialized receptors on the root-like structures of the receiving neuron, known as dendrites (the "post-synaptic" area). Dendrites are covered with receptors that are either excitatory or inhibitory, meaning they are capable of increasing or decreasing the post-synaptic neuron's chance of firing their own action potential and carrying a message further.

Not long ago, the scientific consensus was that the brain's circuitry became hardwired in adulthood. However, a completely fixed system does not lend itself to incorporating new information.

"While the brain doesn't make any new neurons, it constantly adds and subtracts connections between those neurons to optimize our most basic functions," explains Nedivi. Unused synapses are pruned away to make room for more regularly used ones. Nedivi has pioneered techniques of two-photon microscopy to examine the plasticity of synapses on axons and dendrites in vivid, three-dimensional detail in living, behaving, and learning animals.

But how does the brain determine which synapses to strengthen and which to prune? "There are three ways to do this," Littleton explains. "One way is to make the presynaptic side release more neurotransmitters to instigate a bigger response to the same behavioral stimulus. Another is to have the postsynaptic cell respond more strongly. This is often accomplished by adding glutamate receptors to the dendritic spine so that the same signal is detected at a higher level, essentially turning the radio volume up or down." (Glutamate, one of the most prevalent neurotransmitters in the brain, is our main excitatory messenger and can be found in every region of our neural network.)

Littleton's lab studies how neurons can turn that radio volume up or down by changing presynaptic as well as postsynaptic output. Characterizing many of the dozens of proteins involved has helped Littleton discover in 2005, for instance, how signals from the post-synaptic area can make some pre-synaptic signals stronger and more active than others. "Our interest is really understanding how the building blocks of this critical connection between neurons work, so we study Drosophila, the simple fruit fly, as a model system to address these questions. We usually take genetic approaches where we can break the system by knocking out a gene or overexpressing it, that allows us to figure out precisely what the protein is doing."

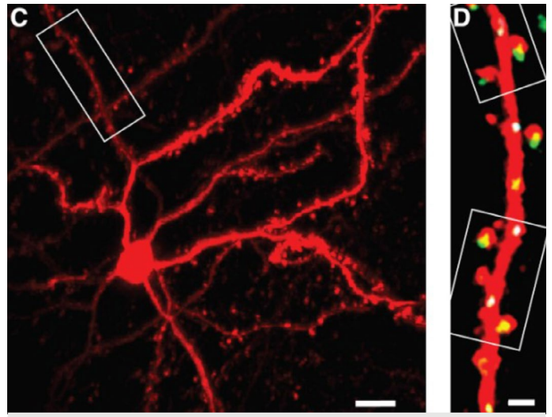
In general, the release of neurotransmitters can make it more or less likely the receiving cell will continue the line of communication through activation of voltage-gated channels that initiate action potentials. When these action potentials arrive at presynaptic terminals, they can trigger that neuron to release its own neurotransmitters to influence downstream partners. The conversion of electrical signals to chemical transmitters requires presynaptic calcium channels that form pores in the cell membrane that act as a switch, telling the cell to pass along the message in full, reduce the volume, or change the tune completely. By altering calcium channel function, which can be done using a host of neuromodulators or clinically-relevant drugs, synaptic function can be tuned up or down to change communication between neurons.

The third mechanism, adding new synapses, has been one of the focal points of Nedivi's research. Nedivi models this in the visual cortex, labeling and tracking cells in lab mice exposed to different visual experiences that stimulate plasticity.

In a 2016 study, Nedivi showed that the distribution of excitatory and inhibitory synaptic sites on dendrites fluctuates rapidly, with the number of inhibitory sites disappearing and reappearing in the course of a single day. The action, she explains, is in the spines that protrude from dendrites along their length and house post-synaptic areas.

"We found that some spines which were previously thought to have only excitatory synapses are actually dually innervated, meaning they have both excitatory and inhibitory synapses," Nedivi says. "The excitatory synapses are always stable, and yet on the same spine, about 70% of the inhibitory synapses are dynamic, meaning they can come and go. It's as if the excitatory synapses on the dually innervated spines are hard-wired, but their activity can be attenuated by the presence of an inhibitory synapse that can gate their activity. Thus, Nedivi found that the number of inhibitory synapses, which make up roughly 15% of the synaptic density of the brain as a whole, play an outsized role in managing the passage of signals that lead to the formation of memory.

"We didn't start out thinking about it this way, but the inhibitory circuitry is so much more dynamic." she says. "That's where the plasticity is."



By staining neurons with three colors under a two-photon microscope Elly Nedivi's lab was able to resolve excitatory (yellow) and inhibitory (white) post-synaptic areas. This figure is from a 2016 study in which the lab revealed that inhibitory synapses sometimes come and go rapidly.

Inside Engrams: Memory Storage & Recall

A brain that has made many connections and can continually edit them to process information is well set up for its neurons to work together to form a memory. Understanding the mystery of how it does this excited Susumu Tonegawa, a molecular biologist who won the Nobel Prize for his prior work in immunology.

"More than 100 years ago, it was theorized that, for the brain to form a biological basis for storing information, neurons form localized groupings called engrams," Tonegawa explains. Whenever an experience exposes the brain to new information, synapses among ensembles of neurons undergo persistent chemical and physical changes to form an engram.

Engram cells can be reactivated and modified physically or chemically by a new learning experience. Repeating stimuli present during a prior learning experience (or at least some part of it) also allows the brain to retrieve some of that information.

In 1992, Tonegawa's lab was the first to show that knocking out a gene for the synaptic protein, alpha-CamKII could disrupt memory formation, helping to establish molecular biology as a tool to understand how memories are encoded. The lab has made numerous contributions on that front since then.

(Continued on next page)

More Learning about Memory

Picower Institute scientists have made **numerous discoveries** about molecular mechanisms of plasticity and memory. Scan the code to browse a whole gallery of research advances by not only the four biology faculty members featured in this story, but also colleagues **Mark Bear**, **Mriganka Sur** and **Li-Huei Tsai** in Brain and Cognitive Sciences.

By 2012, neuroscience approaches had advanced to the point where Tonegawa and colleagues could directly test for the existence of engrams. In a study in *Nature*, Tonegawa's lab reported that directly activating a subset of neurons involved in the formation of memory–an engram–was sufficient to induce the behavioral expression of that memory. They pinpointed cells involved in forming a memory (a moment of fear instilled in a mouse by giving its foot a little shock) by tracking the timely expression of the protein c-fos in neurons in the hippocampus. They then labeled these cells using specialized ion channels that activate the neurons when exposed to light. After observing what cells were activated during the formation of a fear memory, the researchers traced the synaptic circuits linking them.

It turned out that they only needed to optically activate the neurons involved in the memory of the footshock to trigger the mouse to freeze (just like it does when returned to the fearful scene), which proved those cells were sufficient to elicit the memory. Later, Tonegawa and his team also found that when this memory forms, it forms simultaneously in the cortex and the basolateral amygdala, where the brain forms emotional associations. This discovery contradicted the standard theory of memory consolidation, where memories form in the hippocampus before migrating to the cortex for retrieval later.

Tonegawa has also found key distinctions between memory storage and recall. In 2017, he and colleagues induced a form of amnesia in mice by disrupting their ability to make proteins needed for strengthening synapses. The lab found that engrams could still be reactivated artificially, instigating the freezing behavior, even though they could not be retrieved anymore through natural recall cues. They dubbed these no-longer naturally retrievable memories "silent engrams." The research showed that while synapse strengthening was needed to recall a memory, the mere pattern of connectivity in the engram was enough to store it.

While recalling memories stored in silent engrams is possible, they require stronger than normal stimuli to be activated. "This is caused in part by the lower density of dendritic spines on neurons that participate in silent engrams," Tonegawa says. Notably, Tonegawa sees applications of this finding in studies of Alzheimer's disease. While working with a mouse model that presents with the early stages of the disease, Tonegawa's lab could stimulate silent engrams to help them retrieve memories.

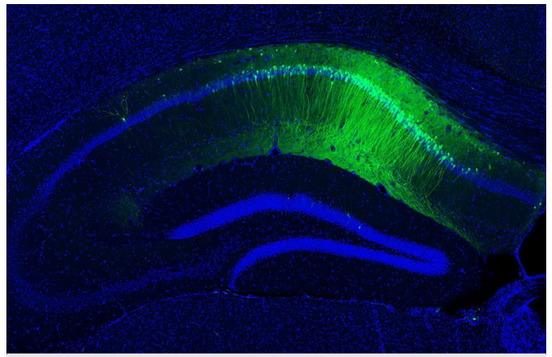
Making memory useful

Our neural circuitry is far from a hard drive or a scrapbook. Instead, the brain actively evaluates the information stored in our memories to build models of the world and then make modifications to better utilize our accumulated knowledge in intelligent behavior.

Processing memory includes making structural and chemical changes throughout life. This requires focused energy, like during sleep or waking states of rest. To hit replay on essential events and simulate how they might be replicated in the future, we need to power down and let the mind work. These so-called "offline states" and the processes of memory refinement and prediction they enable fascinate Matt Wilson. Wilson has spent the last several decades examining the ways different regions of the brain communicate with one another during various states of consciousness to learn, retrieve, and augment memories to serve an animal's intelligent behavior.

"An organism that has successfully evolved an adaptive intelligent system already knows how to respond to new situations," Wilson says. "They might refine their behavior, but the fact that they had adaptive behavior in the first place suggests that they have to have embedded some kind of a model of expectation that is good enough to get by with. When we experience something for the first time, we make refinements to the model–we learn–and then what we retain from that is what we think of as memory. So the question becomes, how do we refine those models based on experiences?"

Wilson's fascination with resting states began during his postdoctoral research at the University of Arizona, where he noticed a sleeping lab rat was producing the same electrical activity in its brain as it did while running through a maze. Since then, he has shown that different offline states, including different states of sleep, represent different kinds of offline functions, such as replaying experiences or simulating them. In 2002, Wilson's work with slow-wave sleep showed the important role the hippocampus plays in spatial learning. Using electrophysiology, where probes are directly inserted into the brain tissue of the mouse, Wilson found that the sequential firing of the same hippocampal neurons activated while it sought pieces of chocolate on either end of a linear track occurred 20 times faster while the rat was in slow-wave sleep.



Green staining in the hippocampus brain region of a mouse shows engram cells involved in storing a memory of experiencing a little foot shock. Blue highlights other cells.

In 2006, Wilson co-authored a study in *Nature* that showed mice can retrace their steps after completing a maze. Using electrophysiological recording of the activity of many individual neurons, Wilson showed that the mice replay the memory of each turn it took in reverse, doing so multiple times whenever they had an opportunity to rest between trials. These replays manifested as ripples in electrical activity that occur during slow-wave sleep.

"REM sleep, on the other hand, can produce novel recapitulation of action-based states, where long sequences and movement information are also repeated." (e.g. when your dog is moving its legs during sleep, it could be producing a full-fledged simulation of running). Three years after his initial replay study, Wilson found that mice can initiate replay from any point in the sequence of turns in the maze and can do so forward or in reverse.

"Memory is not just about storing my experience," Wilson explains. "It's about making modifications in an existing adaptive model, one that's been developed based on prior experience. In the case of A.I.s such as large language models [like ChatGPT], you just dump everything in there. For biology, it's all about the experience being folded into the evolutionary operating system, governed by developmental rules. In a sense, you can put this complexity into the machine, but you just can't train an animal up de novo; there has to be something that allows it to work through these developmental mechanisms."

(Continued on next page)

The property of the brain that many neuroscientists believe enables this versatile, flexible, and adaptive approach to storing, recalling, and using memory is its plasticity. Because the brain's machinery is molecular, it is constantly renewable and rewireable, allowing us to incorporate new experiences even as we apply prior experiences. Because we've had many dinners in many restaurants, we can navigate the familiar experience while appreciating the novelty of a celebration. We can look into the future, imagining similarly rewarding moments that have yet to come, and game out how we might get there. The marvels of memory allow us to see much of this information in real-time, and scientists at MIT continue to learn how this molecular system guides our behavior.

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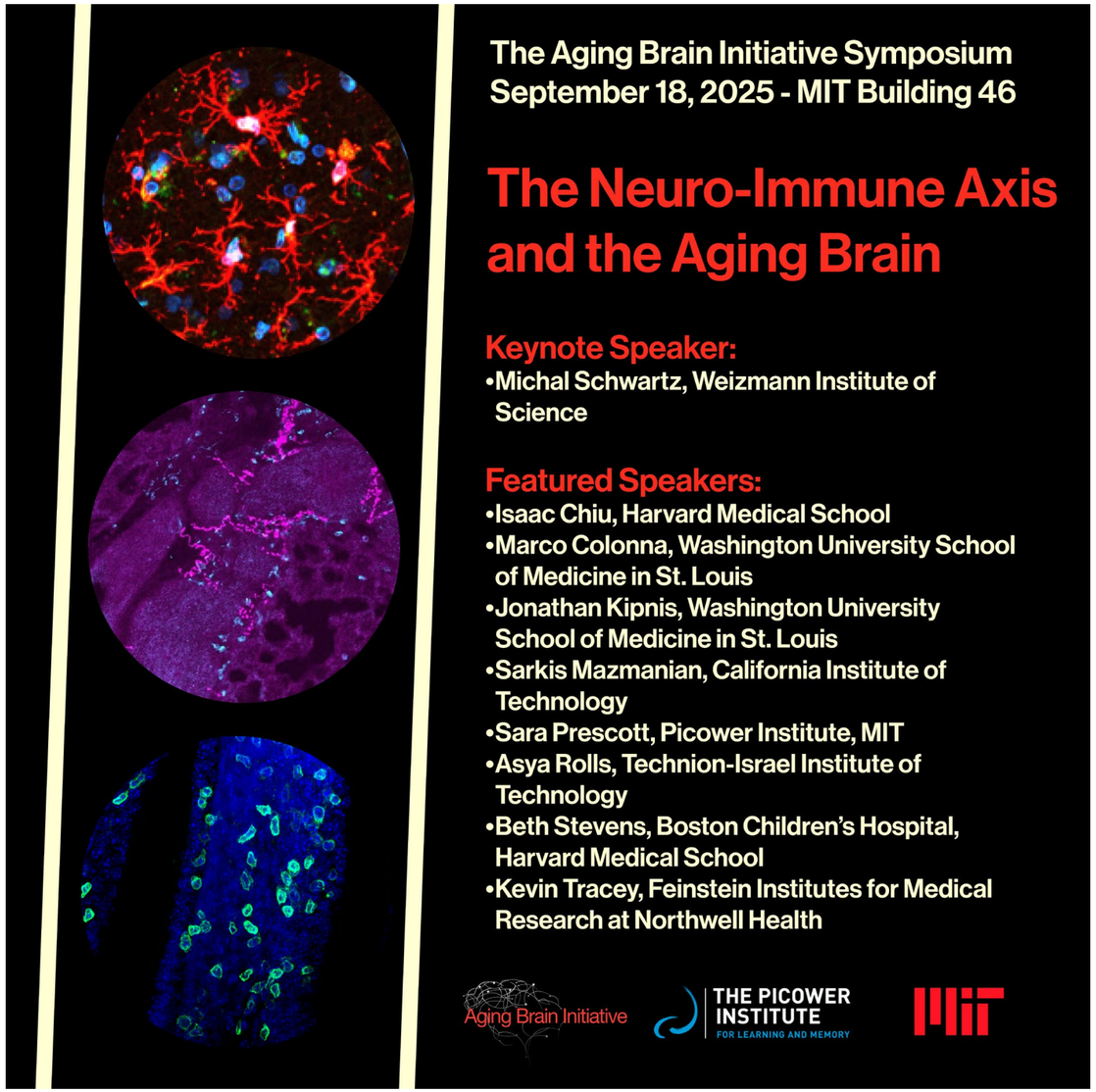

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